KEYNOTE SPEAKER

Genomics and Systems Biology and Emerging Technologies

IN SILICO DESIGN OF IMPROVED CELL FACTORIES – NEW METHODS AND EXPERIMENTAL VALIDATION

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Industrial Biotechnology is increasingly replacing chemical processes in numerous industrial sectors, since it allows the use of renewable raw-materials and provides a more sustainable manufacturing base. The field of Metabolic Engineering (ME) has thus gained a major importance by providing tools for the design of improved microorganisms for industrial applications. Currently, many Metabolic Engineering problems are approached using genome-scale metabolic models, which have a wide variability regarding predictive capacity.
Metabolic model predictions broadly rely upon well performed gene annotations. To aid in that task and in metabolic model reconstruction, we have previously developed the merlin framework, an open source Java software tool, distributed at www.merlin-sysbio.org. The new version of merlin allows to perform automated annotations of enzyme and transport functions, as well as protein localization based on customizable parameters.
Strain simulation is usually performed by using Genome-scale stoichiometric models and Linear or Quadratic Programing methods that assume a steady state over the intracellular metabolites. However, a systematic evaluation of the predictive capacities of the available genome-scale models and simulation tools has not been performed. We have performed a thorough analysis of in vivo data of S. cerevisiae regarding essentiality, flux distributions and auxotrophies and have concluded that many of the available ME tools do not allow to make accurate predictions, ultimately leading to ineffective ME strategies. We also propose novel tools for the reconciliation of experimental data with model predictions.
Finally, as an example of application of in silico metabolic engineering strategies, we have combined the use of genome-scale metabolic models with a multi-objective metaheuristic approach, identifying several gene deletion targets for growth-product coupling of a family of C4-dicarboxylic acids. Four multi-gene deletion strain designs, including the chassis cell and the final producer strains, were implemented and experimentally tested. Thus, we were able to generate pre-optimized backbone strains for enhanced production of different platform chemicals derived from the same metabolic pathways, hence showing that modular design strategies may contribute to accelerate metabolic engineering tasks.